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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,187	07/30/2001	Rosanne M. Crooke	ISPH-0590	2706

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EXAMINER
VIVLEMORE, TRACY ANN

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,187	CROOKE ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,9,10,12,13 and 24-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,9,10,12,13 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.0.0.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments-Claim Rejections - 35 USC § 103

Claims 1, 4-7, 9, 10, 12 and 13 are rejected under 35 USC 103(a) as unpatentable over Stenn et al. in view of and Baracchini et al. and McKay et al. for the reasons of record set forth in the Office Action mailed November 15, 2004.

Applicant's arguments in the remarks submitted March 29, 2004 have been fully considered but are not persuasive. Applicant asserts that in view of the amendment to claim 1 and the cancellation of claims 14 and 15, the 103 rejection is improper because the limitations of the claims are not present in the combination of Stenn et al., Baracchini et al. and McKay et al. This argument is not persuasive because the only limitation not previously present is that the antisense oligonucleotide is targeted to the 3' untranslated region. Baracchini et al. teach at column 9, line 60 through column 10, line 25 that the 3' untranslated region is a desired target of antisense gene inhibition. McKay et al. provide a similar teaching at column 3, line 52 through column 4, line 5.

New Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12 and 24-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibition of human stearoyl CoA desaturase in cells in vitro, does not reasonably provide enablement for inhibition of human stearoyl-CoA desaturase in an animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

1. The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

2. Claim 12 recites a pharmaceutical composition; claim 24 recites use of this pharmaceutical composition for the purpose of treating an animal. While it is accepted that claims to a composition comprising a pharmaceutically acceptable carrier do not require the composition be used as a pharmaceutical, a claim directed to a pharmaceutical composition implies the composition is to be used as a therapeutic in an organism.

3. Claim 24 is directed to a method of modulating expression of stearoyl CoA desaturase in an animal by administering an antisense oligonucleotide targeted to the 3' untranslated region of human stearoyl-CoA desaturase. Claims 25-27 limit claim 24 by

stating the animal is in need of such treatment, the administration is systemic and that the animal has one of several conditions.

4. The specification provides examples wherein chimeric phosphorothioate antisense targeted to a nucleic acid encoding human stearoyl-CoA desaturase inhibited the expression of human stearoyl-CoA desaturase *in vitro* in human cell lines. The specification does not demonstrate any correlation with the inhibition of human stearoyl-CoA desaturase in cell culture and a treatment effect in any animal for any disease or condition associated with human stearoyl-CoA desaturase. The specification does not present any examples wherein antisense targeted to human stearoyl-CoA desaturase was delivered to cells in any organism, or wherein antisense targeted to human stearoyl-CoA desaturase inhibited the expression of human stearoyl-CoA desaturase in cells in any organism. The specification does not provide any examples wherein treatment effects were obtained for any disease or condition, including a condition that involves abnormal lipid or cholesterol metabolism, atherosclerosis or cardiovascular disease using antisense targeted to human stearoyl-CoA desaturase.

5. The specification does not present any guidance on what specific diseases or conditions can be treated using antisense targeted to human stearoyl-CoA desaturase, including specific conditions that involve abnormal lipid or cholesterol metabolism, and specific types of cardiovascular disease, and what cells to target for a particular disease or condition. Although the art recognizes "there is substantial evidence linking SCD (stearoyl-CoA desaturase) activity to a wide range of disorders including obesity, diabetes, cardiovascular disease, skin disease, neurological disorders and cancer.

However, the causal relationships between SCD (stearoyl-CoA desaturase) activity and these various disease states remain unclear." (Ntambi, J. reference AG on PTO form 1449, filed June 4, 2002, page 1551, second column, last paragraph,). Additionally, Ntambi discusses the role of stearoyl-CoA in disease states wherein reduction of stearoyl-CoA is associated with the condition; for example, reduction of stearoyl-CoA activity can cause loss of myelination. The specification has not provided any antisense molecules to upregulate the expression of stearoyl-CoA, as may be required in many diseases and conditions.

6. The state of the art prior art is such that inhibition of gene expression *in vitro* is routine, but *in vivo* inhibition of gene expression at the time of filing and even to the present time is not routine for several reasons, including the problems of delivery, specificity and duration.

7. The problems of nucleic acid based therapies and antisense technology are well known in the art, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, 2000, of record), Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol 1, p. 503-514) and Jen et al. (Stem Cells 2000, of record)). Such obstacles include, for example,

problems with delivery, target accessibility and the potential for unpredictable nonspecific effects.

8. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

9. Opalinska et al. state on page 511 "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

10. Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant inhibition of gene expression, as claimed. The specification provides examples where human stearoyl-CoA desaturase in inhibited in human cell lines, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any organism. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism). For example, Agrawal et al. (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies") states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

11. Given these teachings, the skilled artisan would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. One of skill in the art would not

know how to deliver oligonucleotides to an organism in such a way that would ensure an amount sufficient to modify or inhibit expression of a target gene is delivered to the proper cell.

12. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of inhibiting gene expression using nucleic acids *in vivo* are unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate cell/organ, at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, attenuating or inhibiting expression of a target gene such that the organism exhibits a loss of function phenotype.

13. The specification does not provide the guidance required to overcome the art-recognized unpredictability of using antisense oligonucleotides in therapeutic applications in any organism. The field of antisense therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

14. Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broad claims of inhibiting the expression of human stearoyl-CoA desaturase in any organism as the art of inhibiting gene expression by introducing antisense oligonucleotides into an organism is neither routine nor predictable. In order to practice the claimed invention *in vivo* in all

organisms a number of variables would have to be optimized, including 1). the mode of delivery of the antisense oligonucleotide to an organism that would allow it to reach the targeted cell, 2). the amount of antisense oligonucleotide that would need to be delivered in order to bind a sufficient amount of human stearoyl-CoA desaturase to inhibit expression to a significant degree once it reached the proper cell and 3). ensuring the antisense oligonucleotide remains viable in a cell for a period of time that allows inhibition of gene expression to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each antisense oligonucleotide. While optimization of any single one of these steps may be routine, when taken together the amount of experimentation required becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 12 and 24-27 are not enabled.

15. Removal of the word "pharmaceutical" from the preamble of claim 12 would obviate the rejection against this claim.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
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TV
May 26, 2005

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